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Correlations between behavior, memory, sleep-wake and melatonin in Williams-Beuren syndrome

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HIGHLIGHTS

- 53% of the WBS individuals did not present a melatonin circadian rhythm variation
- WBS individuals presented auditory and visual short-term memory impairments
- 65% of WBS individuals presented an indicative of at least one sleep disorder
- Sleep disorders are correlated with melatonin content and memory in WBS

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ABSTRACT

Williams-Beuren syndrome (WBS), a neurodevelopmental disorder caused by a microdeletion on chromosomic region 7q11.23, presents with peculiar behavioral and neurocognitive phenotypes that are marked by apparently preserved social and communicative abilities, which contrasts with low overall cognitive and particularly visuo-spatial performance. In addition, parents often report complaints of sleep disorders and behavioral problems of unknown cause. Sleep is a biological phenomenon that is modulated by the plasma concentration of melatonin and with influence on behavioral aspects and memory. Thus, this study sought to investigate the behavior, memory and the presence of sleep disorders in WBS and to correlate these factors with each other and with the plasma melatonin content. We used the Child Behavior Checklist for ages 6–18 (CBCL), the digit subtest of the Wechsler scale for auditory memory, the visual sequential memory subtest of the Illinois Test of Psycholinguistic Abilities (ITPA) and the Sleep Disturbance Scale for Children (SDSC). Determination of urinary aMT6s, an indirect measure of plasma melatonin content, was held for 72 h by ELISA, and the analysis of the circadian rhythm of this content was performed by the Cosinor method. The results of the CBCL showed that 87% of the WBS group presented with a clinical score on the overall competence and total behavioral problems. Furthermore, the behavioral problems that were most frequently reported by parents were anxiety and problems of thought. All individuals with WBS presented with impairments in auditory memory and 47% with impairments in visual sequential memory; 65% of the WBS group presented with an indicative of at least one sleep disorder, where respiratory, initiation and maintenance of sleep (DIMS) and hyperhidrosis were the most frequent disorders. The night time aMT6s levels were lower in individuals with WBS when compared with controls; 53% of the WBS group did not present with circadian rhythm variations in aMT6s levels. In addition, there was a negative correlation between the scores of auditory memory and the total score of sleep disorders and between the DIMS and nocturnal aMT6s content. In conclusion, in the present study, individuals with WBS showed a high frequency of behavioral and memory problems, sleep disturbances and no rhythm variation in aMT6s levels. The low melatonin content may be related with sleep disorders in this population, which, in turn, can have an adverse effect on specific cognitive skills such as memory.

1. Introduction

Williams-Beuren syndrome (WBS) is a neurodevelopmental disorder caused by the heterozygous deletion of WBS critical region (WBSCR) 1.5 Mb–1.8 Mb on 7q11.23 in consequence to a non-allelic homologous recombination (NAHR) [9].

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With an incidence of 1:7500 in equal proportion between genders [69], WBS presents with a phenotype that includes typical facial features with flat middle third of the face, micrognatia, protruding ears, prominence and periorbital swelling, anteverted nostrils, long nasal filter and massive lips [9,48].

The intellectual disability, with average values of Intellectual Quotient (IQ) of 55, is a manifestation that is present in most cases. The behavioral phenotype includes impaired performance in both verbal and non-verbal skills [16,56,61], such as auditory and visual memory [59]. In the case of auditory memory, WBS frequently shows alterations in skills, such as background figure, auditory closure, auditory attention, separation and binaural synthesis, and auditory hypersensitivity to high frequencies [8].

Individuals with WBS apparently exhibit good social and communication skills in contrast with poor general cognitive functioning, often having difficulties in formal communication situations that require the following of rules or developing and maintaining focus in conversation [41,54,58,67]. Psychopathologic manifestations, such as fears and phobias, may also occur [10,25], as well as hyperactivity and attention deficit [26,35,52], which, when combined with intellectual disability, resulting in learning problems [23,24,31,47]. Some studies have also associated WBSCR deletions and autism spectrum disorders indicating that behaviors and neurochemical phenotypes typically associated with autism like hyperserotonemia and low melatonin production can occur in WBS patients [70,71].

Another common aspect to consider in individuals with WBS is the presence of severe disorders of the sleep-wake cycle. According to parents, sleep is not effective, as children have great resistance to going to bed, display excessive anxiety, wake up at night and remain sleepy during the day [4]. Several studies have explored the presence of sleep disorders in WBS, indicating that 36–57% of this population present with some form of sleep disorder, such as restless sleep, disorders of onset and maintenance of sleep, awakening, respiratory re-sleep and excessive daytime sleepiness [6,32,33,44,45] regardless of age [32]. The actigraphy showed that these individuals have a lower sleep efficiency, longer sleep onset latency and shorter sleep duration, so while remaining in bed for 9 h at night, the presence of sleep disorders results in excessive daytime sleepiness [32].

Polysomnography shows changes in several stages of sleep: increased activity of slow wave and decreased alpha and sigma activities, reduced sleep time and decreased sleep efficiency, increased eye movements and movement of arms and legs [33,44].

The relationship between sleep and behavioral aspects has been demonstrated in several neurodevelopmental disorders [18,27,68,75,76] and was already hypothesized in WBS [45].

As causes of sleep disorders in this population, nocturia and periodic limb movements in sleep have been considered due to their association with arousals and awakenings [6,17]. Hyperactivity and anxiety are also mentioned as possible candidates [44]. One possibility that has been poorly explored in this population is the abnormal pattern in the synthesis of the hormone melatonin, produced by the pineal gland in the dark phase; melatonin modulates sleep quality because it transduces environmental photoperiodic information [36,50]. In several conditions, melatonin has been linked to improved quality of sleep, behavior, attention and memory [7,15,21,65,72].

Recently, it has been shown that there is no significant difference between the afternoon and bedtime melatonin salivary levels in children with WBS, which indicates a possible blockage in nocturnal melatonin synthesis. This study did not investigate the rhythmicity in this content for continuous days [66].

The present study is the first one that sought to investigate, in the same group of individuals with WBS, the relationship between behavior, memory, sleep disturbances and possible changes in the melatonin rhythm. Our hypothesis is that sleep disorders associated with deficit in melatonin production may be correlated with behavioral changes and memory in WBS.

2. Methods

2.1. Participants

This cross-sectional clinical study was conducted in accordance with regulatory standards of research involving human subjects, approved by the local ethics committee (Process 0548/2012). The study gathered 15 individuals from the Williams Syndrome Brazilian Association with clinical and molecular cytogenetic WBS diagnostics (FISH positive to elastin gene deletion at 7q11.23). The parents of 25 children with WBS were contacted, and all agreed to take part in the study. In this study, 60% of the children were male and 40% were females, aged 6–17 years (mean = 12.1 ± 3.7 months). The control group consisted by 20 individuals with typical development (67% male and 33% female; 11.2 ± 3.9 years-old).

Socioeconomic levels were determined according to the Brazilian Association of Research Companies [1]. The socio-demographic profile of the WBS group showed that 20% of the investigated population was in classification A2, 35% of the population in classification B2, 20% in the C1 class, 20% in the C2 class, and 5% in classification D.

The Full Scale Intelligence Quotient (FSIQ) estimated that subjects with WBS ranged from 44 to 68 points. The Verbal Intelligence Quotient ranged between 46 and 71 points, and the Performance Intelligence Quotient ranged between 52 and 70 points. The estimated values of Intelligence Quotient were established from two verbal subtests (Vocabulary, Similarities) and two execution subtest (Object Assembly and cubes) from the Brazilian version [30] of the "Wechsler Intelligence Scale for Children" (WISC-III) for children ages 6–16 years [74], and the Brazilian version [49] of the "Wechsler adult Intelligence Scale" WAIS-III, for adults ages 16–89 years [73].

For exclusion criteria, individuals who had co-morbidities, were medicated by melatonin or drugs that influence melatonin synthesis, such as β_1-adrenergic antagonists or some flavonoids [15,64], had conditions that could affect sleep such as epilepsy, had problems with tonsils/adenoids or demonstrated hearing or visual impairments were excluded from this study.

2.2. Procedures

2.2.1. Child behavior inventory

The behavioral profiles of individuals with WBS were obtained from the Brazilian version of the "*Child Behavior Checklist for ages four–18*" (CBCL/6–18) as normed by Bordin et al. [13].

This questionnaire is given as a direct interview with parents and consists of 113 items that are related to behavior problems; the informant classifies the behavior as not true or absent (score = zero), partially or sometimes true (score = one), or very true or often true (score = two) over the last six months. The sum of scores allows the evaluator to draw a behavioral profile of the child or adolescent (internalizing problems or externalizing problems) that is derived from an analysis of eight groupings of items: anxious/depressed, attention problems, delinquent behavior, social problems, thought problems, withdrawn, somatic complaints and aggressive behavior.

The raw scores on each factor were transformed into T scores at three levels, representing unaffected to the most severely affected individuals with symptoms ranging from non-clinical to clinical, respectively. The score for the non-clinical category is <67; the score for the borderline category is 67–70, inclusive; the score for the clinical category is >70. For internalizing and externalizing problems, this ratio should be <60 for the non-clinical category, from 60 to 63 for the neighboring category and >63 for the clinical category.

2.2.2. Auditory and visual memory

Auditory and visual sequential memory were investigated consecutively from the subtests "Digits" of the Brazilian version of the Wechsler Intelligence Scale (WISC-III, [30] and WAIS-III, [49]) and the subtest